

Colorectal Cancer: Does It Matter if You Eat Your Fruits and Vegetables?

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Epidemiologists have long regarded vegetables and fruits as key features of a diet associated with a reduced risk of colorectal cancer. In 1997, the American Institute for Cancer Research (1) assembled a panel of leading epidemiologists and basic scientists to review the literature covering the links between all aspects of diet and the causation of all types of cancer. That panel gave its highest rating for degree of scientific certainty to vegetables as a component of diet that would reduce risk of colorectal cancer. For fruits, the evidence is more limited—in fact, the American Institute for Cancer Research panel concluded that no judgment was possible.

In this issue of the Journal, however, Michels et al. (2) report a thoroughly null association between both fruits and vegetables and colorectal cancer risk in a pair of large prospective cohort studies. Their study has several important strengths that make it a valuable contribution to the growing discussion about the role of vegetables and fruits in preventing colorectal cancer. It has the advantages of a prospective study in effectively precluding recall and selection bias. It makes use of data from two separate cohorts, the Nurses' Health Study and the Health Professionals' Follow-up Study, both of which are large and have a substantial

number of cases. The article reflects a comprehensive and detailed analysis of the possible association of fruits and vegetables with risk of colorectal cancer.

Some important limitations to these two cohort studies, however, warrant consideration. Like all epidemiologic studies of diet and cancer, the study by Michels et al. (2) depends on the range of exposure to the food or nutrient of interest within the study population. Compared with other prospective colorectal cancer cohorts that have studied fruits and vegetables (3–8), the study by Michels et al. shows a comparable, perhaps slightly narrower, range of consumption of these foods. But, as in all similar studies to date from North America or Northern Europe, the high end of intake for both fruits and vegetables is not exceptionally high. Only 2% of the Nurses' cohort consumes more than 4.5 servings of vegetables per day; in the Health Professionals' cohort, only 3% consumes more than 3.5 servings

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per day. These studies cannot rule out the possibility that more substantial intake would be associated with lower risk.

We know very little about the measurement error structure for reported fruit and vegetable intake in food-frequency questionnaires (FFQs). There may well be systematic bias (perhaps a tendency toward overreporting) at the individual level, and this bias may be present—and correlated—in both the FFQ and the reference instrument (dietary records or 24-hour dietary recalls) commonly used in calibration studies (9). This correlated individual-level bias may lead to considerably greater relative risk attenuation than has been previously appreciated (10), making modest decreases in relative risk especially difficult to detect. In multivariate energy adjustment models, this problem may be further compounded by the likely error in reported total energy intake.

In their discussion, Michels et al. (2) review the published findings from prospective cohorts of fruit and vegetable intake and colorectal cancer risk (3,5–8) and observe that in no case were the results completely consistent with a reduction in risk for colorectal cancer. They conclude, therefore, that evidence supporting this hypothesis was lacking. We can, however, look at the prospective data in another way: Four (5–8) of the six previously published studies (3–8) *do* show some inverse association (for part of the cohort or certain subgroups of vegetables) between vegetable consumption and colorectal cancer risk.

Where does this leave us? It seems reasonable to conclude, keeping in mind the methodologic limitations of these investigations, that the prospective epidemiologic studies have not yet made a conclusive case that fruit and vegetable consumption is associated with lower risk of colorectal cancer. We eagerly await the data from numerous large prospective studies now in the field in various locations throughout the world. In future epidemiologic studies, highly detailed FFQs targeted specifically to measuring fruit and vegetable intake (in contrast to instruments that assess all dietary components at the same time) may help to reduce measurement error. Identifying unbiased biomarkers of fruit and vegetable consumption would also be of great value. Serum carotenoids have shown some promise in this regard, but the variation in serum response from person to person casts doubt on whether carotenoids can truly be an unbiased marker of fruit and vegetable consumption. Further intake biomarker work is warranted.

Clinical trials may be informative, although the recent Polyp Prevention Trial (11) did not provide any evidence that increased fruit and vegetable consumption lowers the risk of recurrent adenomas. The ongoing Women's Health Initiative may tell us whether increased fruit and vegetable consumption can lower the incidence of invasive colorectal cancer.

While the findings from the study by Michels et al. (2) may cast some doubt on the hypothesis that fruit and vegetable consumption is associated with a lower risk of colorectal cancer, that hypothesis is still very much alive and worthy of continued investigation. Moreover, as Michels et al. indicate, there are still plenty of good reasons to eat our fruits and vegetables. Many of the classic nutrient-deficiency diseases that remain important

causes of premature death and disability in the nonindustrialized world can be prevented by supplementing the diet with a variety of vitamin-rich fruits and vegetables (12). Fruit and vegetable intake is also inversely associated with risk of heart disease and stroke as well as with risk of several different cancers (although the epidemiologic evidence for an association with some of these malignancies is arguably no stronger at the present time than that for colorectal cancer) (1,13–16).

Regardless of how successful we are in generating persuasive evidence that fruits and vegetables can reduce risk of colorectal cancer, these foods will likely continue to have a vital role to play in human health and disease.

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